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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,484	07/21/2005	Yoshihisa Nishibe	26430U	5312

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EXAMINER	
PALENIK, JEFFREY T	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
11/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,484	NISHIBE ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

STATUS OF THE APPLICATION

Receipt is acknowledged of Applicants' Amendments and Remarks filed, filed 14 August 2009, in the matter of Application N° 10/519,484. Said filings are entered on the record. The Examiner further acknowledges the following:

No claims have been added.

Claims 4-5 are newly cancelled.

Claim 1 has been amended. Claims 1, 6 and 17-20 have been amended to indicate that the solid article is "porous", a property which is supported by Applicants disclosure (see pg. 17, lines 18-21).

Claim 1 has been further amended to recite "[a]n autoclaved sterile aqueous suspension comprising ciclesonide and hydroxypropylmethylcellulose wherein the concentration of the ciclesonide after it is autoclaved is 95% or more compared to that before it is autoclaved". Support for the amendment is found in Applicants' disclosure.

No new matter has been added.

Thus, claim 1 now represents all claims currently under consideration.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS) have been filed for consideration.

WITHDRAWN OBJECTIONS/REJECTIONS

Rejections under 35 USC 112

Applicant's amendments to claim 1 is sufficient enough to render moot the indefiniteness rejections under 35 USC 112, second paragraph. Thus, said rejections have been **withdrawn**.

However, it should be noted that, for the purposes of examination on the merits and despite the forgoing amendments, the Examiner continues to interpret the "HPMC" limitation as encompassing all blends of HPMC.

MAINTAINED REJECTIONS

The following rejection is maintained from the previous Office Correspondence dated 14 August 2009 since either the grounds or art on which they were previously set forth continues to read on the amended limitations.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Karlsson et al. (U.S. Patent Publication 2002/0065256) in view of the Material Safety Data Sheet (MSDS) for Metolose 60SH.

Karlsson et al. teaches the ciclesonide and HPMC suspension, as described above. Said teachings from the withdrawn rejection under 35 USC 102(b) are reproduced here for Applicants' convenience:

The composition is taught by Karlsson et al. at claims 7, 9, and 10. Claim 10 teaches a thickening agent which is further defined as including hydroxypropyl methylcellulose (see [0040] and [0041]).

However, Karlsson does not teach the specific grade of HPMC (HPMC 2910) as cited in claim 3. Per Applicants' specification, the claimed HPMC 2910 is also known industrially as Metolose 60SH. Shin-Etsu Co. produces the HPMC of the present invention and provides an MSDS which further provides a Recommended Use for Metolose 60SH as a thickening agent.

Since the ingredient of the composition is the chemically the same, it follows that particular grade of HPMC used is a result-effective parameter that a person having ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to employ the optimal grade hydroxypropyl methylcellulose within the composition in order to best achieve the desired results. Thus, absent some demonstration of

unexpected results from the claimed parameters, optimization of this ingredient would have been obvious at the time of Applicant's invention.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Karlsson et al. and Nagano et al. (WO 01/28563 A1).

The instantly amended claim 1 is directed to an aqueous suspension comprising ciclesonide and hydroxypropylmethylcellulose 2910 which is sterilized via autoclaving and wherein the resulting preparation comprises at least 95% ciclesonide. Per MPEP §2113, product-by-process limitations hold no patentable weight. Thus, regardless of how the instantly claimed ciclesonide-containing aqueous suspension is made sterile, the fact still remains that a sterile ciclesonide-containing aqueous suspension results.

The teachings to Karlsson et al. are discussed above. Again, Karlsson does not expressly teach using HPMC 2910.

The invention practiced by Nagano et al. is directed to an aqueous pharmaceutical composition containing ciclesonide and HPMC, wherein the ciclesonide is dispersed (e.g. suspended in an aqueous medium in the form of solid particles (Abstract). Compositions 1-5 of Example 1, expressly teach aqueous formulations comprising both ciclesonide and HPMC 2910. Ciclesonide concentration of the preparations was evaluated as being 100% (pg. 7, lines 26-34).

It would have been *prima facie* obvious to a person having ordinary skill in the art at the time the invention was made to have added HPMC 2910 to the invention of Karlsson et al. as a form of HPMC to be mixed and sterilized with ciclesonide. As discussed before, absent any evidence to the contrary (i.e. physical or chemical differences between HPMC 2910 and HPMC),

the ordinarily skilled artisan would have been motivated to substitute one compound for the other and would have still had a high expectation of successfully arriving at the instantly claimed invention.

RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claim 1 under 35 USC 103(a) as being unpatentable over Karlsson et al. in view of the Material Safety Data Sheet (MSDS) for Metolose 60SH, as well as being unpatentable over Karlsson et al. in view of Nagano et al., have both been fully considered, but neither is persuasive.

Applicants argue that a *prima facie* case of obviousness has not been established "because there is no apparent reason to prompt a person of ordinary skill in the art to combine the elements disclosed in the cited references". Applicants further allege that any *prima facie* case of obviousness is rebutted by the data presented. Applicants direct the Examiner's attention specifically to Table 3 on page 14 and Example 2 of the present specification as evidence that the instantly claimed composition achieves an improvement in content uniformity over preparations using other wetting agents.

In response, the Examiner respectfully submits that Applicants' amendment to independent claim 1 and remarks thereto, continue to be unpersuasive. First, the combined teachings above discuss ultimately arriving at a sterile suspension of ciclesonide and HPMC. Karlsson does not expressly teach the sterilization of the formed suspension. However, steam sterilization of its components is suggested ¶[0009]. It is further taught that the individual glucocorticoids are heat sterilized at a temperature ranging from 110-130°C ¶[0019] and that they

are most preferably 99.2% by weight pure. Formation of stable suspensions is discussed in ¶¶[0040] and [0041] being mixed with a preferred wetting agent: HPMC. The ordinarily skilled artisan would have been highly motivated to arrive at the instantly claimed sterile, autoclaved suspension, particularly since Karlsson suggests steam sterilization for the components. Additionally, while Karlsson does not expressly teach the claimed order for combining the components and then sterilizing the suspension, it would have been *prima facie* obvious to a person of ordinary skill in the art that there is no patentable distinction between Applicants' composition and the composition which is taught in the prior art. The selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results. *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) Selection of any order of mixing ingredients is also held to be *prima facie* obvious. *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (see MPEP 2144.04 (IV)(C.)) Furthermore, the Office does not have the facilities for examining and comparing Applicants' ciclesonide/HPMC suspension with that of Karlsson in order to establish that the prior art does ***not*** possess the same material structural and functional characteristics (e.g. content uniformity) of the claimed composition. In the absence of evidence to the contrary, the burden is upon the Applicants to prove that the claimed products/methods are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). As such, it is not absolutely clear that the composition of Karlsson and the instant composition are completely different products as alleged by Applicants.

Lastly, regarding Applicants' purported unexpected results, which are reported in the form of drug content uniformity or uniform drug concentrations, the Examiner, though having reviewed the data, remains respectfully unconvinced. Applicants allege that the instantly claimed ciclesonide/HPMC suspension achieved unexpectedly superior content uniformity results as compared to suspensions comprising other wetting agents." Example 2 and Comparative Examples 3-7 (Table 3), as discussed before differ only in the wetting agent used, Example 2 using HPMC. However, in reviewing the data, it appears that similar content uniformity results (e.g. greater than or equal to 95%) from the different upper, middle and lower portions of the bulk suspensions were acquired, particularly Comparative Example 6. As such, the data on which Applicants rely to demonstrate the critical feature(s) of the instant invention, in actuality demonstrates that other compounds (e.g. hydroxypropyl cellulose) may be used as functionally equivalent wetting agents.

Thus, for these reasons, Applicants' arguments are found unpersuasive. Said rejection is **maintained**.

NEW REJECTIONS

In light of Applicants' remarks and amendments to claim 1, the following rejection has been newly added:

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Nagano et al. (WO 01/28563 A) and Suzuki et al. (JP 2001-048807; English Machine translation) and in further view of the Wikipedia entry for difluprednate.

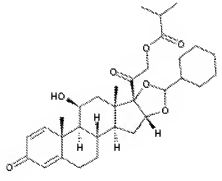
The limitations of claim 1 are discussed above.

Nagano expressly discloses an aqueous pharmaceutical composition comprising ciclesonide and HPMC, specifically HPMC 2910, wherein the ciclesonide is dispersed in an aqueous medium in the form of solid particles. Nagano further teaches that HPMC 2910 not only avoids the variations in the concentration of ciclesonide but may also function as a stabilizing component (Abstract, pg. 4, lines 31-35). The teachings of Nagano do not expressly discuss sterilizing the instantly claimed composition. However, Suzuki remedies this deficiency.

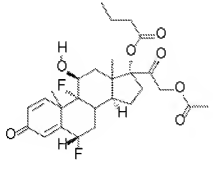
The teachings of Suzuki et al. are directed to preparing an aqueous formulation by dispersing an acetyl-based active ingredient and an additional ingredient such as a water-soluble polymer (e.g. HPMC) (see claims 1, 2 and 4). Acetyl-based active ingredients which are taught as being available include corticosteroids such as difluprednate and budesonide. Regarding the means for achieving sterility, paragraph [0015] further teaches that the practiced formulations may undergo heat sterilization processing such as the pressurization of heat sterilization (e.g. autoclaving). Thus, it follows that drugs having acetyl substitutions such as difluprednate, and

which are mixed with water-soluble polymers such as HPMC, demonstrate the ability to withstand sterilization processes which employ high heat and pressure, such as autoclaving.

Thus, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time invention was made to have prepared an aqueous suspension of ciclesonide and HPMC and sterilize it via autoclaving. The ordinarily skilled artisan would have been motivated to combine HPMC with a drug such as ciclesonide, particularly in view of the teachings of Suzuki, which clearly demonstrates the ability of a water-soluble polymer such as HPMC to stabilize ciclesonide through its stabilization of difluprednate. Both corticosteroid compounds share very similar core ring structures, including bonding two acetyl groups bound at the same point on the 5-membered ring of the structure, as shown below:



Ciclesonide



Difluprednate

Given the ability for difluprednate to be stabilized as discussed above, it stands to reason that the ordinarily skilled artisan would be highly motivated to admix and sterilize an homologous compound such as ciclesonide and arrive at a similar result: a stable sterilized suspension.

All claims under consideration remain rejected; no claims are allowed.

CONCLUSION

Due to the new grounds of rejection, this action is deemed **non-final**.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner, Art Unit 1615